

A Systems Approach for Bioengineering*

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Biomedical and biological engineers differ from other engineers in that they must consider not just the abiotic components of a system but the biotic components as well. While this difference may appear to be obvious, it is the implications of this relationship that define the fields. These engineered systems exhibit a number of defining traits including the necessity for homeostasis on the part of a living system, the interactions between the biological component and the engineered system, and the responses of the organisms to each other. At the University of Maryland we teach a course entitled 'Biological Responses to Environmental Stimuli' to develop an understanding on the part of the students of these relationships and their implications to biological engineers.

SYSTEMS IN BIOENGINEERING

A CRITICAL GOAL of bioengineering education is the introduction of the student to some of the techniques necessary to apply engineering problem solving to living organisms and systems. A classic approach to engineering problem solving is reticulation, breaking the object of study down into a series of networked components. The identified components are then examined and the implications of their arrangement studied. This approach has been used successfully in a wide variety of engineering systems, including diffusion [1], lung dynamics [2], biomedical instrumentation design [3], heat transfer [4], and pharmacokinetics [5]. The crux of the systems approach is that description of complex systems requires understanding of the nature of the individual components, how they are networked together, and how they interact with each other.

Bioengineering (whether biomedical engineering or biological engineering) arose from the need to create and modify systems that include one or more living elements, whether the elements are bacteria, humans, or entire ecosystems. A systems approach is important to bioengineering, whether biomedical or biological. Biomedical and biological engineers differ from other engineers in that they must consider not just the abiotic components of a system but the biotic components as well. While this difference may appear to be obvious, it is the implications of this relationship that defines our field.

If the design engineer fails to consider all of these elements, the success of the result (for example, a suture material) will be negatively impacted. Therefore, bioengineering students must learn to apply classical engineering concepts in profoundly new ways and to a breadth of biological systems not found in any other engineering discipline. For

instance, while energy balances are common in engineering, bioengineering students must perform these balances on species ranging from humans to lizards and, then, consider their effects on behavior. Whether students model water transport through an aquifer or through a cell membrane, bioengineers must consider not just the animate, and the inanimate, but how they mold each other. Furthermore, they must learn the techniques to apply their understanding to the development of predictive physical and mathematical models.

One approach for teaching bioengineering students how to deal with these relationships is through a 'systems approach'. In this approach, students are introduced to biological systems through a series of examples in which interactions between living things and their environment are described. Furthermore, as bioengineering teachers, we must persuade that living things differ substantially from other elements of their engineering design. We must demonstrate that a living material and its environment are inextricably linked, that they must be considered as a system. Furthermore, the students should be encouraged to make the transition between a theoretical and a fundamental understanding of this systems approach.

THE TRAITS OF BIOLOGICAL SYSTEMS

Because of the diverse applications of bioengineering, graduates from bioengineering programs are likely to encounter new systems throughout their careers. Thus, they are likely to benefit from a structure for analysis of biological/engineered systems.

Fully describing these bioengineered systems requires that a number of system properties be considered. Three of these properties are:

- the variability intrinsic in the living elements in a design;

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- the necessity for homeostasis on the part of a living system;
- the tendency of a living system to return to a stable, possibly new, configuration when perturbed.

By considering each of these traits in order, a learning structure can be built. In this structure, the student's understanding of bioengineering systems design and analysis is built in a series of discrete stages, each stage depending on the previous [6].

Biological variability

During their first two years of course work, students receive a general foundation in engineering, physics, and mathematics. In general, the systems that they study are both linear and well behaved. Bioengineers also receive their initial biology courses during this period. Many of these early biology courses are more aimed at describing biological processes than teaching students problem solving. Thus, most students have not been exposed to the variability of biological systems.

One of the most important differences between biological engineering and other engineering disciplines is this inherent variability in biological systems. Often this variability is an order of magnitude greater than that found in, for instance, electrical engineering. It is critical that bioengineers have a fundamental understanding of the stochastic nature of the data on which they will base their analyses. Designs involving living systems must include compensation for this variability. We have found that an effective method for explaining this variability is to describe the process of data acquisition and analysis. Once students understand the nature of this process, they understand the limitations of the data that they use to create a design and/or perform an analysis.

Homeostasis

The second major building block of biological systems analysis and design is the necessity to maintain at least the living portion of the system in homeostasis/steady-state. While living systems are both variable and dynamic systems, they have a very limited operating range. For example, humans have a very limited range of acceptable body temperatures. Therefore, they respond to changes in their environment or activity level in such a way that thermal homeostasis is maintained. Failure to do so results in damage and, potentially, death. Bioengineering students must be taught how to handle the balances required to maintain a system in homeostasis before they can consider the effects of perturbing the system from that balance.

Perturbation from homeostasis

The final building block is to consider the effect of these perturbations. These perturbations typically come from one of two sources. Either the environment surrounding the organism changes or

other organisms interact with an organism of interest.

In the first source, we examine the responses of biological systems to environmental perturbations. One of the unique considerations of biological systems is that they are self-organizing and self-correcting. That is to say that, if a biological system is sufficiently close to a stable point, it will move towards stability. In the case of the human thermal system, it will correct by either increasing heat losses (e.g. sweating) or heat generation (e.g. shivering).

Another relationship that one must consider is the effect of the living system on the engineered system. Many organisms have extensive capability to alter the systems with which they interact. Living systems continuously change in response to their environment, but they also change that environment. Therefore, bioengineering studies must emphasize a systems approach to problem solving. Successful designs only result when an engineer considers not only the individual components of the system but their interactions as well. For example, when one considers the human body's response to the presence of an implant, such as a resorbable suture, one must consider (1) the chemical and physical properties of the suture material, (2) the biological, physical and chemical properties of the tissue being sutured, (3) the impact of the suture on the tissue (the foreign body reaction), and the degradative effects of the surrounding tissue on the suture [7, 8].

The examples must also cover biological responses over a wide range of time frames. For example, in our discussion of the body's responses to extreme heat, we begin with the development of the equations describing the process. However, we then examine the immediate and long-term local and systemic effects of the burns. During the discussion on the foreign body response we discuss the healing processes and how the body responds to the tissue damage, first in the absence of an implant (e.g. healing from a burn or other physical trauma) and second in response to the chronic presence of an implant. During the discussion of the evolutionary adaptations of organisms to mechanical stress, we consider the multiple adaptations of sessile marine organisms to moving water and compare these adaptations to those of trees adapting to winds.

In the second perturbation source, bioengineers must consider how living systems respond to the presence of other living systems, for example population dynamics. Historically, population dynamics has been the domain of the field ecologist. It is therefore of interest to the bioengineers in the environmental and ecological engineering disciplines. However, an understanding of cellular growth kinetics is becoming increasingly important to biochemical engineers. Our engineers consider the effects of unbounded population growth, the limiting effects of the environment on population growth, and interspecies effects such as parasitism,

competition, and predation. On the biomedical end, population kinetics evidence themselves in problems such as the culture of epidermal cells for use in artificial skin and multibacterial strain infections surrounding biomedical implants. In the biotechnology arena, an attempt is often made to maintain bacterial populations in log-phase growth to maximize product production rates [9, 10].

TEACHING TOOLS

Students learn differently. This is particularly true as student bodies become more diversified. The engineering classroom often contains students with a wide range of ages, life experiences, ethnicities, and cultures. Some of these students learn quite quickly in a classroom environment, while others learn more effectively from books or hands-on materials. This is particularly true when the material is conceptually difficult, such as the concept of systems. Because of the difficulties in conveying the concept of systems to students, we have found substantial benefit from the use of multiple teaching tools. The use of multiple, simultaneous methods of content delivery allows reinforcement of the content. In addition to classroom discussion and lecture, we have had success using three other methods of content delivery. These are model development, numerical modeling and simulation, and the use of a 'living laboratory'.

Model development

A good opening to the topic of biological systems is an examination of processes involved in model development and verification. The skill of model development is especially important to bioengineers. In practice, they are often called to examine systems for which no model has been previously developed or to adapt an existing model to a new system.

We have found that a useful structure begins by developing a nonmathematical model for the system. This approach allows identification of the

relevant variables and fluxes early in the analysis process. Furthermore, generating a 'picture' model of the system helps the students to visualize the processes. Having this visualization also helps students to predict potential and reasonable outcomes. Such a series of drawings is shown in Fig. 1.

Using the identified variables and fluxes, differential equations can either be developed directly or from an analogous system. The data acquisition process is then described along with the process conversion of raw data to equations and coefficients suitable for inclusion in the model. Our experience is that many undergraduate students are not familiar with the concept of curve fitting and the limitations that these fits place on the design of biological systems models. Finally, we compare the analytical results with the outcomes that the students devise during the visualization exercise. This comparison is used to determine whether the model is reasonable or not. Typically, we demonstrate this modeling process with an example where several modeling iterations are required.

Numerical modeling

Engineering students often absorb concepts effectively when they are given the information in a dynamic, visual mode. For complex systems it is also helpful if they are allowed to manipulate the system and see how it responds. With the development of graphical modeling software, students have the opportunity to move directly from the analogous system to a simulation. The choice of software is dependent on the analogy that you wish to use. For instance, the use of bond graphs is supported using 20-Sim (Controllab Products B.V., Netherlands) or CAMP-G (CADSim Engineering, Davis, CA). Electrical analogies are supported using Pspice (OrCAD, Beaverton OR). We have had excellent results using block diagram analogies using *Simulink* (The MathWorks, Inc., Natick, MA).

This direct translation provides several advantages and disadvantages. The first advantage is

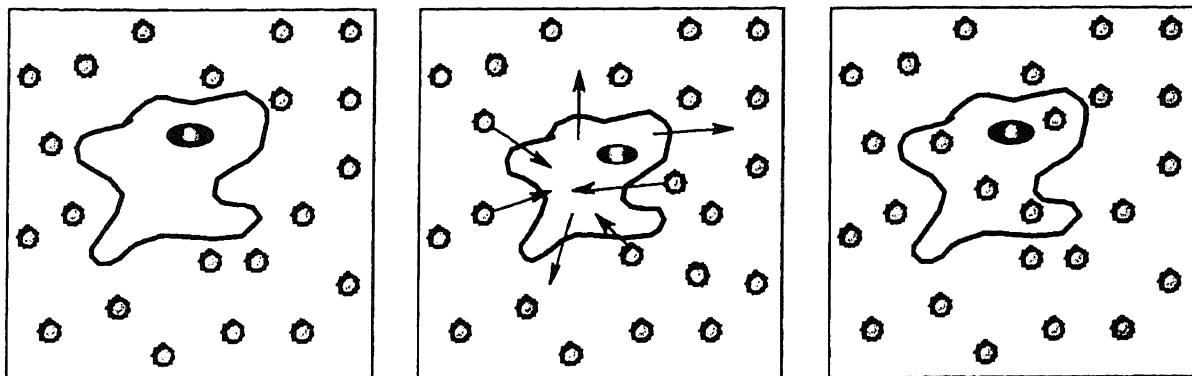


Fig. 1. An example of picture model showing the response of a cell to the addition of a cell membrane permeating solute. In the first schematic, the solute is added. In the second the flow of water from the cell and the movement of solute into the cell is shown. In the final schematic, the solute has permeated the cell and the cell has moved to a new equilibrium.

that the software is often substantially easier to learn and use. Thus, students are more likely to try alternative possibilities out than they are with either programs or numerical analysis software such as *MATLAB* (The MathWorks, Inc., Natick, MA) or *Mathematica* (Wolfram Research, Inc., Champaign, IL). Second, the use of analogous systems [9] helps establish the commonality of analysis techniques across multiple domains (e.g. electrical, diffusional, mechanical). Finally, most graphical modeling languages support graphical output. This allows the students to see the results of their modeling experiments. The disadvantages, while outweighed by the advantages, include (1) the cost of the software is often in the range of thousands of dollars, even with academic licenses, (2) the students try to solve problems by 'fiddling' with the model rather than by analyzing the problem, and (3) the students become dependent on university computing facilities that are often much more extensive than those in the workplace.

Laboratory experimentation

While quite common in biological sciences programs, engineering students only rarely have the opportunity to work with living materials in their courses. This hands-on experience is an essential part of training competent bioengineers, since it helps to establish the advantages and limitations of modeling biological systems. Students are often profoundly affected by the practical demonstration of these limits. They quickly realize that living organisms can not be rebooted if they make an error. Therefore, they tend to be much more careful in the design of their processes. This care helps to integrate the model development and validation process within the students though patterns. Throughout this process, the students learn to design experiments, make measurements based on their experimental design, and revise the design based on the information gathered.

COURSE ELEMENTS

In the Biological Resources Engineering program at the University of Maryland, one of the primary courses in which the systems concept is conveyed is a senior level course entitled 'Biological responses to environmental stimuli'. In this course we demonstrate that living materials and their environment are inextricably linked, that they must be considered as a system. Students are encouraged to make the transition between a theoretical and a fundamental understanding of this systems approach. We approach this process in two parallel tracks, a traditional classroom setting and a nontraditional laboratory. In the classroom setting an emphasis is placed on the development of engineering models to describe biological processes and on the description of examples of the systems under consideration.

Data acquisition, analysis, and model development

The opening topic 'Biological Responses to Environmental Stimuli' is an examination of processes involved in model development and verification. The classroom discussion of model development is supplemented by problems in which the students are asked to go through the model development process and perform various curve-fitting techniques and regressions. The curve fitting is performed using *MATLAB* and the regression is performed using *Excel* (Microsoft Corporation, Redmond, WA).

Homeostasis

The second major concept that we convey in the course is that of homeostasis/steady-state. The primary system examined during the classroom portion of this concept delivery is the thermoregulatory system in humans. To illustrate the homeostasis concept, we perform thermal balances around human beings under a variety of environmental conditions and human activities. We consider the possible modes for energy transfer between the human body and its environment. The heat losses must then be balanced against metabolic heat production.

Perturbations from homeostasis

In the course's final topic, we cover a wide variety of examples. These examples include burns, wound healing and the foreign body reaction, toxicology, electromagnetic effects on the human body, the effects of fluid movement on sessile organisms, and population dynamics and modeling.

Living laboratory

In our living laboratory, the emphasis is on the experiment design and practical implementation of systems with living components. The premise of the exercise is that, if students truly understand the requirements of living creatures, they can keep those animals alive and healthy. Over the last few years, this laboratory has involved the design of an ecosystem with the ability to support 2 to 4 crayfish in a sealed (airtight, watertight, but light admitting) system. Several factors influenced the decision to use crayfish in the laboratory. The factors include (1) their lack of vertebra reduces the number regulations that apply to their handling [11], (2) their size (3 to 7 cm in length) is such that they are easily handled by students, and (3) they are extremely tolerant of nonideal water quality [12]. The written components include a design proposal, a progress report, a final design report, and an independent document describing their design to the general public.

In the beginning of this laboratory, the students are asked to identify critical variables for the support of these animals and to decide if, when, and how they should be measured. This decision-making process moves from a thought experiment to a physical process and the students are asked to

design the data sheets and make the measurements on the crayfish and their environment. During this time the crayfish tanks are not sealed and the students are asked to examine the open system. While some guidance is provided (primarily in the form of advice regarding known pitfalls) the students are free to make their own decisions.

Next, the students set up their ecological microcosms and try to stabilize them. During the initial phases of setup, the students watch the tank parameters, such as ammonia and pH, begin to change. The rates of these changes slowly decrease as the ecosystem begins to self-organize. During these laboratories, the students become aware of the complexity of their challenge. As the self-organization proceeds, environmental variables within the microcosm become inextricably linked. For example, one common problem is that the dissolved oxygen within in the tank begins to drop. Crayfish can survive wide ranges in dissolved oxygen. However, there is a distinct behavioral response. The crayfish alter both their location (moving towards the water surface) and reduce their activity level. Students typically respond by purchasing additional aquarium plants at the local pet store and placing the plants in the tank. This approach, however, is flawed. These plants are often in poor health and, instead of adding oxygen-producing capacity, begin to die and decay, thus consuming oxygen.

Next, the students develop an airtight seal for their tanks and then seal the tanks. Requiring that the students seal the tanks for steadily increasing periods (1, 2, and 4 weeks) gives the students the opportunity to examine the microcosm's response to the perturbation, identify the problem's source(s), and redesign the system. Requiring these iterations ensures that the students actively consider the processes occurring in their systems. It is not uncommon for the system to go unstable

within a day or two in the first design iteration. Often the system crashes to a degree that the students abort their experiment, rebuild their ecosystem, and reseal. However, after several iterations the students develop systems that are quite stable and support the crayfish over increasingly longer periods.

This iterative phase of the laboratory lasts until the end of the course. The iterative failure and redesign cycle results in stronger designs [13] and increasing student confidence in their design abilities. We have also found that the students thoroughly enjoy the opportunity to work in an open laboratory, where they control the experimental structure.

CONCLUSIONS

In a wide range of biological engineering problems, the design process depends upon the engineer's understanding of the unique responses of biological organisms to their environment. This can only be achieved if the students develop an understanding of their designs as systems. These systems respond significantly differently from the isolated parts.

This understanding is achieved through four phases (1) familiarization of the students with the process of data acquisition and analysis, including an understanding of the processes used in converting raw data to a set of equations (2) development of the concept of homeostasis with respect to living materials, (3) elaboration of the effect of their environment on living materials, and (4) description of the interactions between living things. In our program these phases are successfully achieved through a combination of laboratory experiences and classroom instruction.

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